Enteral *Versus* Parenteral Feeding

Effects on Septic Morbidity After Blunt and Penetrating Abdominal Trauma

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To investigate the importance of route of nutrient administration on septic complications after blunt and penetrating trauma, 98 patients with an abdominal trauma index of at least 15 were randomized to either enteral or parenteral feeding within 24 hours of injury. Septic morbidity was defined as pneumonia, intra-abdominal abscess, empyema, line sepsis, or fasciitis with wound dehiscence. Patients were fed formulas with almost identical amounts of fat, carbohydrate, and protein. Two patients died early in the study. The enteral group sustained significantly fewer pneumonias (11.8% *versus* total parenteral nutrition 31.%, $p < 0.02$), intra-abdominal abscess (1.9% *versus* total parenteral nutrition 13.3%, $p < 0.04$), and line sepsis (1.9% *versus* total parenteral nutrition 13.3%, $p < 0.04$), and sustained significantly fewer infections per patient ($p < 0.03$), as well as significantly fewer infections per infected patient ($p < 0.05$). Although there were no differences in infection rates in patients with injury severity score < 20 or abdominal trauma index ≤ 24, there were significantly fewer infections in patients with an injury severity score > 20 ($p < 0.002$) and abdominal trauma index > 24 ($p < 0.005$). Enteral feeding produced significantly fewer infections in the penetrating group ($p < 0.05$) and barely missed the statistical significance in the blunt-injured patients ($p = 0.08$). In the subpopulation of patients requiring more than 20 units of blood, sustaining an abdominal trauma index > 40 or requiring reoperation within 72 hours, there were significantly fewer infections per patient ($p = 0.03$) and significantly fewer infections per infected patient ($p < 0.01$). There is a significantly lower incidence of septic morbidity in patients fed enterally after blunt and penetrating trauma, with most of the significant changes occurring in the more severely injured patients. The authors recommend that the surgeon obtain enteral access at the time of initial celiotomy to assure an opportunity for enteral delivery of nutrients, particularly in the most severely injured patients.

DESPITE DIAGNOSTIC AND therapeutic advances available to physicians, sepsis remains the most common problem in critically ill patients. The hypermetabolic state induced by these complications gradually depletes the body of fat and protein stores. This progressive protein-calorie malnutrition increases the rate and risk of infection[1] and impairs wound healing.[2] Over the past 2 decades, significant amounts of clinical and laboratory research have focused on the role of specialized nutrition support in preserving lean tissue mass and host defenses. Although clinicians agree that the gastrointestinal (GI) tract is the preferable route for nutrient administration, patients are often provided total parenteral nutrition (TPN) because of ease and reliability of administration. Unfortunately, this "traditional" approach has been no panacea for the critically ill, and few studies demonstrate significant benefits on morbidity and mortality rates with TPN.

A substantial body of data suggests that route of nutrient administration influences the response to injury. The normal well-fed intestine absorbs nutrients while maintaining an effective barrier against intraluminal toxins and bacteria. Peristalsis, secretory immunoglobulin A, mucin, and the mucosa have protective and supportive roles in maintaining this function.[3] Proponents of enteral (ENT) feeding cite expense, preservation of gut mass,[4] and positive effects on the metabolic, hormonal,[5] immunologic,[6] and visceral protein responses to injury with feeding[7] but these arguments are countered by difficulty with delivery of adequate nutrients by nasoenteric feeding and the rare but possible risk of life-threatening complications. Direct ENT feeding by jejunostomy provides a more reliable means of ENT access and intestinal feeding that bypasses the problem of delayed gastric emptying. Although laboratory[8,9] and prospective clinical trials[10,11] confirm reduced morbidity and mortality rates after trauma when

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nutrients are provided through the GI tract rather than intravenously (I.V.), many clinicians remain skeptical of this route of administration.[12] Unfortunately, in the few randomized prospective studies to date, the most severely injured patients such as those requiring early reoperation, massive blood transfusions, or those with extensive intra-abdominal injuries with an abdominal trauma index (ATI)[13] of greater than 40 have been excluded from analysis.[10,11] If ENT feeding is truly beneficial, the most critical patients should be included in the study population.

This randomized prospective study examines the effect of early ENT *versus* early parenteral feeding on the outcome of trauma patients in the first 15 days of hospitalization. Using these two standard feeding techniques, outcome variables included the amount of nutrition delivered, septic morbidity rates, and clinical outcome in a population of consecutive trauma patients with an ATI ≥ 15 treated at an urban level I trauma center.

Materials and Methods

Study Protocol

Ninety-eight trauma patients admitted to the Presley Memorial Trauma Center at the University of Tennessee, Memphis, requiring an emergent laparotomy between December 1989 and August 1991, were enrolled in the study protocol. Patients 18 years of age or older, with an intra-abdominal injury requiring laparotomy, who sustained an ATI of at least 15, were included in the study. After the management of intra-abdominal injuries, jejunostomy tubes were inserted distal to the ligament of Treitz using either a needle catheter jejunostomy (Vivonex Kit, Norwich-Eaton Pharmaceuticals, Norwich, New York) or standard red rubber catheter chosen at the discretion of the five trauma service surgeons. Within 8 hours after operation, the Nutrition Support Service of the Regional Medical Center of Memphis was consulted and patients were assigned to either ENT or TPN feeding using a randomization table generated by computer before institution of the study. Patients were not excluded from the study because of excessive blood loss, the need for reoperation within the first 72 hours, or an ATI of 40 or greater. Patients with intestinal repairs or anastomosis were included in the study. All postoperative management was directed by three of the operating surgeons responsible for trauma intensive care unit care. The study design and consent was approved by the Institutional Review Board of the University of Tennessee, Memphis.

Non-nutritional management of patients for both intra- and extra-abdominal injuries remained standard for our institution throughout the study. Patients sustaining blunt or penetrating trauma were explored for signs of peritoneal irritation or hemodynamic instability from continued intra-abdominal bleeding. Standard diagnostic peritoneal lavage criteria were used (red blood cells ≥ 100,000/mm^3, white blood cells > 500/mm^3, presence of fiber, bacteria, or bile) to assess abdominal injury. When computed tomography scans were performed to evaluate blunt abdominal trauma, patients were explored for class III or higher liver and spleen injuries. Patients with gunshot wounds that traversed the abdominal cavity or knife stab wounds that penetrated the anterior fascia underwent celiotomy. Perioperative broad-spectrum antibiotics were administered prophylactically to all patients for no more than 5 days unless clinical evidence of infection ensued or prophylactic antibiotics were dictated by the specialty services. Skin and subcutaneous tissue were left open for delayed primary closure in the presence of fecal and significant gastric contamination.

Both ENT and parenteral nutrients available to the clinician at the Regional Medical Center at Memphis are determined biannually by a bidding process that defines the formulary for nutrient products. The ENT formula (Vital HN, Ross Laboratories, Columbus, OH) administered to patients in this randomized, prospective study was chosen because it was the low-bid ENT product at the start of this study. For pair feeding purposes, the pharmacy provided a parenteral formula with similar concentrations of protein (Travasol, Clintec Nutrition, Deerfield, IL), carbohydrate, and fat (Intralipid, Kabivitrum, Inc., Alameda, CA) (Table 1). Institution of full-strength formulas progressed toward a goal rate of 1.5 to 2.0 g/kg/day of protein/amino acids and 30 to 35 Kcal/kg/day of nonprotein calories (NPC). The time from injury to institution of feeding was noted, and the rates of ENT and TPN feeding advanced as tolerated by the clinical condition of the patient. Eight patients with coagulopathy and uncontrollable intra-abdominal bleeding had temporary packing of their intra-abdominal injury and subsequent correction of hypothermia, acidosis, and coagulopathy in the intensive care unit. These eight patients were returned to the operating suite within 24 to 48 hours for completion of their operations and placement of ENT feeding tubes and they were subsequently randomized to either ENT or TPN feeding.

Nasogastric decompression continued for at least 3 days. Nursing personnel flushed jejunostomy tubes with 10 cc of saline every 8 hours and administered no med-

TABLE 1. *Composition of Enteral and Parenteral Formulas*

	Enteral	Parenteral
Protein/amino acids	16.7%	17%
BCAA	18.2%	15.6%
CHO	73.9%	74%
Fat	9.4%	9%
Calorie/nitrogen	150/1	150/1

BCAA, branched-chain amino acids; CHO, carbohydrate.

ications other than tube feeding through the jejunostomy. The sole exception to this protocol occurred in six (four TPN/two ENT) patients with *Candida* colonization at multiple sites. In those patients, nystatin was administered through the jejunostomy catheter and immediately flushed with 10 mL saline. Central venous catheters were changed over a guidewire every 3 days, and the catheter tip and subcutaneous portions were sent for semiquantitative cultures. Twenty-four-hour urine collections were obtained on days 1, 4, 7, and 10 from the first 25 patients admitted to the trauma intensive care unit. Venous blood sampling for SMA-24 was obtained on the same days. The operating surgeon calculated the ATI at the time of the initial jejunostomy placement. Nursing personnel of the Trauma Center Registry calculated the Injury Severity Score (ISS) to provide an anatomic index of the severity of total body injury.

Septic morbidity was defined as pneumonia, intra-abdominal abscess (IAA), empyema (EMP), or line sepsis during the first 15 days. Septic morbidity was limited to 15 days for several reasons. Sixty-two (64%) patients had been discharged from the hospital by that time. Of the remaining patients, most who developed pneumonias, IAAs, or EMPs had developed this complication within the first 2 weeks. Late septic complications that might have developed were related to orthopedic complications, recurrent urinary tract infections, or recurrent pneumonia. There is no reason to expect that early ENT feeding would have any effect on these complications.

Pneumonia was defined as fever, leukocytosis, positive sputum/bronchoalveolar lavage specimens, or purulent sputum with the development of new pulmonary infiltrates. Atelectasis, pulmonary contusion, and pleural effusions were excluded as causes of the source of infiltrates. Intra-abdominal abscess or EMP was defined as the presence of a purulent collection in the abdominal or thoracic cavity after drainage by laparotomy, thoracostomy tube, or computed tomography–directed catheter placement. Line sepsis was defined as purulence at the exit site of the catheter or positive catheter tip cultures in association with positive blood cultures and no other obvious source of bacteremia. Patients were not discontinued from TPN because of line infection; however, the catheter was removed and nutrition was reinstituted within 24 hours by a catheter inserted into another site. Necrotizing fasciitis, and wound infections associated with wound dehiscence were considered septic complications; however, minor wound infections and urinary tract infections were not included. Diarrhea was defined as unformed, watery stool occurring three or more times per 24-hour period.

Enteral nutrition continued in ENT patients until they tolerated a diet, but two patients were switched to TPN because of failure to tolerate at least 50% of nutrient goal by 1 week. The complications of these patients were included in the ENT analysis. After the first 40 patients had been enrolled in the study, TPN patients developing pneumonia, EMP, or IAA were switched to ENT feeding after confirmation of infections. In this group also, outcome data and septic morbidity that occurred up to the time of the switch to ENT feeding was included in the TPN group data. No enrolled patients were dropped from study analysis except for two early deaths.

All infections were treated after diagnosis by the surgeons delivering the postoperative care. At the time of hospital discharge, all charts were reviewed by the principal author for confirmation of infection. The charts of those patients in whom the presence of infection was not clear were reviewed by a second surgeon blinded to therapy, and this determination was considered definitive for the presence or absence of infection. After discharge, charts were reviewed to determine length of hospital stay, number of ventilator days, number of days receiving tube feedings or TPN, number of antibiotics and number of days on antibiotics, failure of ENT nutrition requiring cross-over to TPN, number of units of blood administered in the first 24 hours and during total hospitalization, and the maximum bilirubin level occurring in the first 15 days. The amount of nutrition administered by the ENT and TPN routes was also obtained. Nitrogen balances were calculated on days 1, 4, 7, and 10 by subtracting nitrogen losses (total urinary nitrogen excreted over 24 hours) plus an estimated stool and obligatory nitrogen loss of 2 g from the total nitrogen administered during that 24-hour period. Total urinary nitrogen was calculated using the pyrochemiluminescence technique with the Antek Nitrogen Analyzer (Antek Inc., Houston, TX).

Statistical Analysis

Significance for discrete (categorical) variables was determined with the chi square test of homogeneity or Fisher's exact test; all continuous variables were tested with either t tests or Mann-Whitney U tests. Before making each t test, we tested the assumption of equal or unequal variances with an F test and used the appropriate t test. Two-way analysis of variance was used to assess differences for infected and noninfected patients, for rate per kilogram per day, and ISS and ATI scores. A repeated measures analysis of variance compared nitrogen balance over time. Kaplan-Meier estimates of the survival distribution were computed within strata for length of stay in the hospital and number of feeding days and tested for equality. Risk was estimated as the cumulative incidence among patients who developed infections during the first 15 days of hospitalization. The crude measure of association between a single potential risk factor and infection was expressed as the relative risk, or rate of risk. Logistic regression was used to evaluate results from univariate and multivariate analyses and approximate relative risk by odds ratios. For multivariate analyses, patients were stratified by presence (or absence) of a particular injury, mechanism of injury, or severity of injury (ISS or ATI score).

Results

Ninety-eight patients entered the study. One death occurred within 4 days in each of the groups due to hemodynamic instability and progressive multiple system organ failure. These two patients were excluded from analysis. Groups were well matched for severity of injury, age, and mechanism of injury (Table 2).

Although not statistically significant, more patients (31.4%) in the ENT group sustained blunt trauma than in the TPN group (22.2%). Only six patients suffered knife wounds, with four of these patients entered into the TPN group.

Enteral feeding began 24 ± 1.7 hours after surgery; TPN began 22.9 ± 1.6 hours after surgery. Two patients (3.9%) failed ENT feedings because of significant abdominal distention. One patient developed delirium tremors and significant abdominal distention, but no significant pathology was found at exploration. He subsequently suffered dehiscence of his wound and developed the only IAA in the ENT group. The second patient developed abdominal distention and failed to tolerate a minimum of 25 mL/hour, therefore I.V. feeding was begun 7 days after entry into the study. Seven TPN patients were switched to ENT feeding after developing significant infections after operation.

There were no significant differences in blood requirements during the first 24 hours, total blood administered during the hospitalization, days on a ventilator, number of antibiotics, or number of days on antibiotics (Table 3). Patients in the TPN group had significantly higher maximum bilirubin levels during the first 15 days (ENT: 1.6 ± 0.3 mg/dL *versus* TPN: 2.2 ± 0.04 mg/dL, $p < 0.05$), although no significant differences in maximum bilirubin serum concentrations were noted between either the infected ENT and infected TPN group (ENT: 3.2 ± 1.5 mg/dL *versus* TPN: 3.4 ± 1.0 mg/dL) nor between the uninfected ENT and TPN groups (ENT: 1.4 ± 0.3 mg/dL *versus* TPN: 1.6 ± 0.3 mg/dL).

TABLE 2. *Demographics and Mechanism of Injury*

	ENT (N = 51)	TPN (N = 45)	p
Age (yr)	30.4 ± 1.7	30.6 ± 1.4	NS
ATI	29.1 ± 1.8	29.1 ± 1.4	NS
ISS	25.1 ± 1.7	25.1 ± 1.9	NS
LOS (days)	20.5 ± 2.8	19.6 ± 2.8	NS
Mechanism of injury			
Blunt	16 (31.4%)	10 (22.2%)	NS
Penetrating	35 (68.6%)	35 (77.8%)	NS
Gunshot	30 (58.8%)	29 (64.4%)	NS
Knife	2 (3.9%)	4 (8.9%)	NS
Shotgun	3 (5.9%)	2 (4.4%)	NS

Mean ± SEM.
ENT, enteral; TPN, total parenteral nutrition; ATI, abdominal trauma index; ISS, injury severity score; LOS, length of stay.

TABLE 3. *Antibiotics, Blood Administration, Ventilator Needs, and Nutritional Administration*

	ENT	TPN	p
Blood (1st 24 hr)	6.1 ± 1.2 units	6.1 ± 1.2 units	NS
Blood (total)	8.9 ± 1.5 units	9.6 ± 2.1 units	NS
Ventilator days	2.8 ± 0.7	3.2 ± 1.0	NS
No. of antibiotics	2.6 ± 0.3	3.0 ± 0.6	NS
Days on antibiotics	10.9 ± 1.6	11.4 ± 2.3	NS
Nitrogen balance (mg/kg/day)*			
Day 1	−284 ± 25 (16)	−252 ± 24 (20)	NS
Day 4	−77 ± 28 (19)	−109 ± 29 (21)	NS
Day 7	−238 ± 51 (11)	−149 ± 37 (11)	NS
Day 10	−171 ± 34 (5)	−190 ± 66 (5)	NS
NPC/kg/day	15.7 ± 4.2	19.1 ± 3.3	<.05
NPC/kg at maximum rate	29.0 ± 1.5	31.7 ± 1.2	NS

Mean ± SEM.
* No. of patients analyzed for nitrogen balance shown in parentheses.
ENT, enteral; TPN, total parenteral nutrition; NPC, nonprotein calories.

There were no significant differences in nitrogen balances between the two groups on any day. Nitrogen balances became more negative during the later days of study as less extensively injured patients were transferred from the intensive care unit. Enteral nutrition patients received significantly less nutrition per kilogram per day than did TPN patients ($p < 0.05$), but no differences in maximal rates given were noted between the two groups or in the noninfected patients (ENT: 30.2 ± 1.2 NPC/kg/day *versus* TPN: 29.9 ± 15 NPC/kg/day). Infected ENT patients tended to get less nutrition during the study (ENT: 27.7 ± 2.8 NPC/kg/day *versus* TPN: 33.7 ± 1.9 NPC/kg/day), but this failed to reach statistical significance ($p = 0.09$).

Patients randomized to ENT experienced significantly less septic morbidity than patients receiving TPN. Enteral nutrition patients developed significantly fewer pneumonias, abscesses (defined as IAA or EMP) or line sepsis (Table 4). Only one patient with line sepsis did not have a simultaneous pneumonia, IAA, or EMP, so that the addition of line sepsis increased the number of infected ENT and TPN patients by one in each group. Enteral patients sustained significantly fewer infections per patient than the TPN group (0.25 ± 0.06 *versus* 0.71 ± 0.14, $p < 0.03$) as well as significantly fewer infections per infected patients (1.08 ± 0.08 *versus* 1.6 ± 0.8, $p = 0.04$). Only three ENT patients developed more than one infection,

TABLE 4. *Septic Morbidity*

Sepsis	ENT	TPN	p
Pneumonia	6/51 (11.8%)	14/45 (31%)	<.02
Intra-abdominal abscess	1/51 (1.9%)	6/45 (13.3%)	<.04
Empyema	1/51 (1.9%)	4/45 (9%)	NS
Line sepsis	1/51 (1.9%)	6/45 (13.3%)	<.05
Fasciitis/dehiscence	3/51 (5.9%)	4/45 (8.9%)	NS
Abscesses (intra-abdominal and/or empyema)	2/51 (3.9%)	8/45 (17.8%)	<.03
Pneumonia and/or abscesses	8/51 (13.7%)	17/45 (37.8%)	<.02
Pneumonia, abscesses, and/or line sepsis	9/51 (15.7%)	18/45 (40%)	<.02

ENT, enteral; TPN, total parenteral nutrition.

TABLE 6. *Frequency of Infections (Pneumonia, Intra-abdominal Abscess, or Empyema) After Stratification of Patients by Mechanism and Severity of Injury*

	ENT	TPN		
Variable	No. (%)	No. (%)	Odds Ratio	p
ISS ≤ 20	3/17 (17.7)	4/20 (20.0)		0.9
ISS > 20	5/34 (14.7)	13/25 (52.0)	6.3 ×	<0.002
ATI ≤ 24	5/24 (20.8)	7/24 (29.2)		0.6
ATI > 24	3/27 (11.1)	10/21 (47.6)	7.3 ×	<0.005
ATI > 24 and ISS > 20	3/20 (15.0)	8/12 (66.7)	11.3 ×	<0.003
Blunt	4/16 (25.0)	6/10 (60)	3.0 ×	0.08
Penetrating	4/35 (11.4)	11/35 (31.4)	3.6 ×	<0.05

ENT, enteral; TPN, total parenteral nutrition; ISS, index severity score; ATI, abdominal trauma index.

whereas 14 of 45 parenteral patients developed more than one infection (p = 0.02) (Table 5). All patients with fasciitis/dehiscence had a simultaneous pneumonia or abscess.

If one considers only the presence of pneumonia, IAA, or EMP as a source of infection, ENT feeding has its most beneficial effect in the most severely injured patients, but has little effect in less injured patients (Table 6). No significant differences in infection rates were noted in patients with an ISS of 20 or less. Of patients with a high ISS (>20), five of 34 (14.7%) of ENT patients developed an infection *versus* 13 of 25 (52.0%) of the TPN group (p < 0.002); failure to administer ENT feeding to this population of patients increased the risk of septic complications by a factor of 6.3. In patients with an ATI > 24, use of TPN was associated with a sevenfold increase in the risk of infection, with an incidence of 11.1% (3/27) with ENT feeding *versus* 47.6% (10/21) with TPN (p < 0.005). In the 32 patients with both high ISS (> 20) and high ATI (> 24), TPN usage was associated with an 11-fold increase in the risk of infection, with a 15% infection rate (3/20) with ENT feeding *versus* 66.7% (8/12) with TPN feeding (p < 0.003). Patients with blunt injuries had higher infection rates if fed parenterally (6/10; 60%) than if fed enterally (3/6; 18.8%), with TPN feeding associated with a threefold increased risk of infection, but this barely failed to reach statistical significance (p = 0.08). Enteral patients with penetrating wounds developed significantly fewer (p < 0.05) septic complications than did TPN patients, with the risk of infection increased 3.6 times in the TPN group. If infection is limited to pneumonia, IAA, or EMP, there was no difference between infected ENT and TPN groups in ATI (ENT: 30.6 ± 4.6 *versus* TPN: 34.4 ± 3.2) or ISS (ENT: 29.1 ± 4.1 *versus* TPN: 32.9 ± 2.9).

Evaluating outcome by organs injured, significant differences in the infection rates between ENT and TPN were found in patients with pancreas or liver injuries (Table 7). There was no significant difference in infection rate with treatment in patients when stratified by colon/rectal, kidney, stomach or duodenal, vascular, or splenic injuries, although both splenectomy and stomach injury approached statistical significance.

Similar trends were noted in the patients excluded from previous clinical trials (Table 8). Twenty patients recruited had an ATI ≥ 40 (n = 14; seven ENT, seven TPN), required more than 25 units of blood during the first 24 hours (n = 4; three ENT, one TPN), had a pelvic fracture requiring more than 6 units of blood (n = 3; two ENT,

TABLE 5. *Frequency of Infections*

	ENT	TPN
Number of Infections/Patient	No. (%)	No. (%)
0	39/51 (76.5)	25/45 (55.6)
1	9/50 (17.7)	6/45 (13.3)
2	0	6/45 (13.3)
3	0	4/45 (8.9)
4	3/51 (5.9)	3/45 (6.7)
5	0	1/45 (2.2)

ENT, enteral; TPN, total parenteral nutrition.
p = 0.02.

TABLE 7. *Frequency of Infections (Pneumonia, Intra-abdominal Abscess, or Empyema) After Stratification of Patients by Individual Injuries*

	ENT	TPN		
Injury	No. (%)	No. (%)	p	Odds Radio
Colon/rectum	3/21 (14.3)	5/17 (29.4)	NS	
Stomach	4/16 (25)	9/16 (56.3)	<0.08	4.0 ×
Duodenum	1/3 (33.3)	4/8 (50.0)	NS	
Pancreas	2/11 (18.2)	4/5 (80)	<0.02	18.0 ×
Liver	3/21 (14.3)	14/29 (48.3)	<0.02	5.6 ×
Spleen	0/5 (0)	3/6 (50)	<0.07	2.0 ×
Kidney	3/9 (33.3)	3/8 (37.5)	NS	
Vascular	2/12 (16.7)	2/8 (25.0)	NS	

ENT, enteral; TPN, total parenteral nutrition.

TABLE 8. *Demographic Characteristics and Outcome of Patients With ATI > 40, Blood Loss > 25 Units in the First 24 Hours, Pelvic Fracture With > 6 Units Blood Loss, or Reoperation Within 72 Hours*

	ENT (n = 11)	TPN (n = 9)	p
ATI	40.5 ± 5.9	42.7 ± 6.9	NS
ISS	22.9 ± 2.8	29.7 ± 3.9	NS
Blunt injuries	3/11	2/9	NS
Penetrating injuries	8/11	7/9	NS
ISS > 20/≤ 20	6/5	7/2	NS
ATI ≥ 24/< 24	8/3	7/2	NS
Blood (1st 24 hr)	15.3 ± 3.8 units	11.6 ± 3.5 units	NS
Blood (total)	20.6 ± 4.0 units	20.6 ± 7.6 units	NS
Bilirubin maximum	2.3 ± 0.8 mg/dL	4.6 ± 1.8 mg/dL	NS
Length of stay	36.6 ± 9.4 days	28.7 ± 9.3 days	NS
Days on nutrition	12.4 ± 1.6	12.2 ± 1.7	NS
Colon injuries	7/11	4/9	NS
Pancreatic injuries	3/11	4/9	NS
Liver injuries	4/11	8/9	<0.03
Septic morbidity			
Pneumonia	2/11	5/9	NS
Intra-abdominal abscess	1/11	3/9	NS
Empyema	0/11	2/9	NS
Pneumonia or abscess (intra-abdominal or empyema)	3/11	7/9	0.07
Infections/patient	0.4 ± 0.2	1.2 ± 0.3	0.03
Infections/infected patient	1.0 ± 0	1.6 ± 3.0	<0.01

ENT, enteral; TPN, total parenteral nutrition; ATI, abdominal trauma index; ISS, injury severity score.

one TPN), or required reoperation within the first 72 hours (n = 8; six ENT, two TPN). Although there were no significant differences in blood requirements, length of stay, days on nutrition, maximum bilirubin, or individual infections between the two groups (Table 7), three of 11 ENT patients developed either a pneumonia, IAA, or EMP, *versus* seven of nine TPN patients; this almost reached statistical significance (p = 0.07) for this small group of patients. Patients receiving TPN experienced significantly more infections per patient and infections per infected patient.

Enteral feeding was not risk free, and several complications were directly related to this route. One patient in the ENT group required reoperation because of a small bowel obstruction at the jejunostomy site. This complication was totally preventable and was caused by inappropriate suturing of the jejunostomy up to the anterior abdominal wall so that the jejunal loop was reversed, causing a closed loop obstruction. Significantly more patients developed diarrhea with ENT feeding than with TPN feeding (11/51 *versus* 7/45, p < 0.01).

Discussion

The ideal clinical study randomly assigns a homogeneous population of patients to various treatment arms with prospective evaluation of outcome, excluding a few patients from the final data analysis. Although trauma patients cannot be considered a homogeneous population, they have in common a hypermetabolic response to injury, acute deterioration in lean body mass, and a high rate of septic complications. In the present study, whether septic morbidity is defined as pneumonia, IAA, or EMP, ENT feeding improved the clinical outcome of multiply injured patients.

We believe that the current prospective study provides conclusive evidence of the beneficial effect of ENT feeding in injured patients. Only two patients enrolled in the study were subsequently excluded from analysis because of early deaths. The randomized prospective methodology produced groups comparable in age, severity of injury, mechanism of injury, and blood transfusions. One can argue that the ENT population was, in fact, the slightly more injured group. Enteral patients had a higher percentage of colon, pancreatic, and blunt injuries, as well as a greater number of patients with ISS > 20 and ATI > 24 or both. Despite this, the ENT population experienced significantly less septic morbidity, including fewer infections per patient and significantly fewer infections per infected patients. Only three of 15 ENT patients sustained multiple infections, whereas 14 of 45 TPN patients had two or more infections. Most of these septic processes were either pneumonia or abscess (EMP or IAA). Neither EMP nor pneumonia could be explained on the basis of chest tube placement because 19 of 51 ENT and 14 of 45 TPN patients had chest tubes inserted soon after admission. Empyemas developed in only four of the 14 TPN patients and none of the ENT patients with chest tubes, whereas pneumonias developed ipsilateral to the chest tube in four of the TPN group and two of the ENT group. Line sepsis was a significant problem, particularly in the TPN group, probably because of the prolonged insertion, because central lines in ENT patients were removed as soon as possible. All central catheters at our institution are multiple lumen, and previous work[14,15] demonstrated a 20% sepsis rate when TPN is administered through multiple-lumen catheters. Line sepsis had a minor impact on the ultimate rate of septic morbidity; five of six patients with line sepsis in the TPN group had a simultaneous pneumonia or abscess during the course of the study.

There were no significant differences in length of stay, number of antibiotics, number of days on antibiotics, or ventilator days. One might expect shorter hospital stays and fewer antibiotic needs in the less infected ENT population. Some of this may be related to the high incidence of blunt injuries in the ENT population, which prolonged hospital stays because of associated orthopedic and neurosurgical injuries requiring prolonged bed rest, skeletal traction, or delays in placement. Antibiotic days or number of antibiotics were not different between the two groups because of prophylactic administration for open fractures, orthopedic and neurosurgical invasive procedures, and invasive intracranial monitoring. Because of the high incidence of prophylactic antibiotic coverage in noninfected individuals, no significant differences could be ascertained.

"When the gut works, use it" is a commonly expressed dictum, but clinicians are often dissuaded by the difficulties involved in providing ENT nutrition or the extra minutes necessary at the operating table to gain ENT access. Particularly in the intensive care unit population, it is easier to infuse nutrition through existing indwelling central lines than to deal with diarrhea, bloating, and frequent interruptions in feeding. This is reflected in significantly less nutrients administered per kilogram body weight during the course of the study in the ENT population, although ultimate maximal rates were similar between the two groups. It appeared it was not merely the amount of nutrition or NPC administered to the patient, but more importantly, the route through which the nutrition was administered. Identical formulas cannot be given I.V. and enterally because the human GI tract cannot tolerate the hyperosmolar load found in TPN solution. Although some difference in amino acid profiles may exist between the two solutions, similar amounts of protein, carbohydrate, and fat were administered to both groups. Enteral and TPN feeding of identical solutions has been tolerated in animal models, and the beneficial effects of gut processing of nutrients in a population prone to septic morbidity seems well supported by both laboratory and clinical experience.

Although the explanations for beneficial effects of ENT nutrition are elusive, the first clue that ENT feeding might be important in the response to and recovery from infectious challenges appeared in a series of experiments from Sheldon's laboratory, using a model of septic adjuvant peritonitis. Peterson, Sheldon, and Carpenter[16] noted increased mortality rate with protein-calorie malnutrition as well as with I.V. feeding. In subsequent experiments,[8,9] Kudsk et al. noted that both malnourished and well-nourished animals pair fed identical nutrient solutions enterally and parenterally survived the septic peritonitis better when nutrients were given through the GI tract. At approximately the same time, Alexander et al.[17] demonstrated that burned children randomized to receive a normal protein or high protein ENT diet sustained fewer septic episodes and a lower mortality rate when receiving more ENT protein. Border et al.[18] also correlated a reduced rate of sepsis with increased ENT delivery of protein. Moore et al. studied trauma patients randomized to early postinjury ENT nutrition compared with delayed[10] or immediate[11] I.V. nutrition support and also noted a higher incidence of IAA[10] or pneumonia[11] in the TPN group. A blunted acute phase protein response and higher levels of constitutive proteins also occurred during ENT feeding.[7] In a meta-analysis of several smaller, randomized prospective studies of ENT *versus* TPN feeding, Moore et al.[19] found that blunt trauma patients fed enterally experienced the most significant reduction in septic complications, a finding consistent with our data, although, in addition, our study demonstrated a lower incidence of septic complications after penetrating trauma.

To understand potential mechanisms, laboratory studies have focused on changes in mucosal structure, permeability to bacteria and toxins, gut immunology, and bacterial colonization. In rats, starvation[20] and I.V. feeding[4,21] produce dramatic histologic changes, primarily in the proximal intestinal mucosa, with loss of villus height, cellular proliferation, mucosal protein, and overall mucosal mass. Mucosal permeability to macromolecular markers increases with I.V. feedings[22] and starvation.[23] The gut mucosa, however, remains an effective barrier to intraluminal bacteria after starvation unless an inflammatory stimulus is simultaneously administered.[24] A small amount of ENT feeding quickly reverses this barrier defect.[25] The gut barrier is permeable to bacteria with I.V. TPN[6] unless the I.V. nutrition is supplemented with a specific gut fuel, glutamine.[26] Glutamine attenuates mucosal atrophy in TPN rats, although the mucosal thickness is still significantly less than that achieved with normal ENT nutrition.[27] Because glutamine released by skeletal muscle increases significantly with stress and sepsis, Wilmore et al.[28] postulated this as an endogenous protective mechanism to support the fasted gut.

Route of nutrient administration affects GI immunologic barriers. Parenteral feeding decreases biliary concentrations of secretory immunoglobulin A, with recovery occurring in animals fed enterally[29] but not in those fed parenterally, unless the I.V. TPN was supplemented with glutamine.[26] Others have noted that depressed *in vivo* lymphocyte responses after femur fracture in rats recovers with ENT but not with I.V. feeding.[30]

Despite the proliferation of laboratory data, changes in GI tract integrity to bacteria has not been proven in clinical experience. Although mesenteric lymph nodes do contain viable bacteria after bowel obstruction,[31] and gut permeability to lactulose and mannitol measured by urinary excretion increases after acute[32] and chronic[33] burns, Moore and colleagues[34] could not demonstrate bacterial translocation in the portal vein of trauma patients in whom portal vein catheters had been inserted for sequential blood sampling. This may be a problem of sampling site because translocation primarily occurs through the lymphactics, which could allow bacteria to pass through the thoracic duct and be cleared by the pulmonary vasculature, resulting in an increase in pneumonias; no data currently exist that test this hypothesis. Positive blood cultures occur after hemorrhagic shock, but there is poor correlation with the subsequent development of septic complications.[35]

Enteral nutrition is not without risk, and complications ranging from abdominal distension[36,37] to frank necrosis[38] have been reported, In the current study, patients received fewer calories through the GI tract and developed more diarrhea, documenting the difficulty in providing an "ideal" amount of ENT nutrition. In addition, one patient required re-exploration when the jejunostomy had been constructed, folding the small bowel back on itself and causing a closed loop obstruction.

The cause of increased infection in our TPN group is multifactorial, and we can only speculate that ENT feeding improves the status of the gut immune system, restores normal gut architecture and microflora, and aids the mucosa in withstanding challenges to these systems. It is unclear, in fact, whether ENT feeding improves the rate of septic morbidity or whether TPN itself causes an increase in septic complications. In the recent Veterans Administration cooperative study[39] of malnourished patients randomized to perioperative nutrition *versus* early surgery, a significant increase in septic complications, including pneumonia and line sepsis, occurred in patients with a mild or moderate malnourished state who were randomized to perioperative TPN. Müller et al.,[40] in a randomized prospective study of perioperative nutrition in patients with cancer, dropped a third arm of therapy in which patients received TPN with 50% of NPC as I.V. fat because of an unusually high rate of septic complications. These studies suggest that I.V. feeding may increase susceptibility to the development of infection.

Although the explanation is unknown, there appears to be little doubt that ENT processing of nutrients provides some beneficial effect when compared with TPN, at least in the more severely injured (ATI $\geq$ 24 or ISS $>$ 20) patients. Many of the less injured patients would have recovered with no complications even without nutrition support. Because of strong sentiment for some nutrition in our patient population, we could not justify randomization to a nonfed group in this protocol. This may or may not be defensible, particularly in patients with an ATI $\leq$ 24 or ISS $<$ 20. Further protocols investigating mechanisms might be limited to only those patients with more severe injuries.

In summary, it is as yet unresolved whether ENT feedings make things better, parenteral feedings make things worse, or both, but clinicians should not ignore ENT access at the initial operation and feeding because the price paid is an increase in septic complications. Whether no nutrition produces results superior to TPN, or equal or superior to ENT feeding, is unknown. Mechanisms have yet to be defined, but the principles appear to be well supported: obtain ENT access at the time of surgery to assure an opportunity for ENT delivery of nutrients, particularly in the most severely injured patients.

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Discussion

DR. J. DAVID RICHARDSON (Louisville, Kentucky): Drs. Bland and Jones, I apologize for rising again. I think it is an excellent study that Drs. Kudsk and Fabian and their associates have done. When Ken asked me to discuss it, I told him that he should know I was basically skeptical of this whole concept and that perhaps it might be better to get somebody else. And he said, "Well, it might be good to have at least one skeptic." I have read the paper, and I think one cannot help but be intrigued by what certainly looks like a very strong association toward decreased infections with enteral feeding, or at least the converse of increased infections with total parenteral nutrition (TPN). Such data would support other papers on the subject, such as that by Moore and Moore from Denver, and would fit nicely into the experimental work, I guess, on bacterial translocation if one is inclined to believe in that entity. Dr. Neal Garrison of our institution has done some superb work in his laboratory in which he has shown that enteral feeding increases mucosal blood flow and, therefore, increases hepatic blood flow. Certainly, that would have theoretical benefits in dealing with patients who have the potential for sepsis.

I do believe, however, that we must analyze these data very carefully before we accept the premise that every patient with a potential major injury should have a jejunostomy tube put in at the time of initial operation. There are a lot of things that do not make sense to me from my experience in taking care of patients who are fed by a variety of methods; I cannot clinically ever tell the difference in who is going to have infection and who is not. I guess I am not convinced that there are sufficient data with most trauma patients to say that we can really prove that any nutritional support is really necessary. If one looks at the pneumonia problem, in the manuscript, the authors say that they dealt with the problem of the confusing chest x-ray by eliminating patients who had pulmonary contusion and atelectasis. Quite simply, I do not understand how you do that. Every day when I look at patients who have fuzzy-looking chest x-rays, I do not know whether they have contusion, fluid overload, or pneumonia. At the patient's bedside, determining who has pneumonia and who does not is an extraordinarily hard call. If you change two patients either way, 14 *versus* 6, you get an NS there instead of a 0.02, and you did not get on the program.

Secondly, line sepsis was a major problem. The authors made a point, however, that clearly the patients with TPN are most likely to get line sepsis, and that seems intuitive. I think we need to think about the fact that perhaps it is the line sepsis inducing other infectious problems. Patients who, once they develop a line sepsis, seem to then develop other surgical types of infection.

Thirdly, I just wonder why enteral feedings would decrease the incidence of empyema or fascitis? Even if one believes in bacterial translocation and believes that increased mucosal blood flow is important, why would that make the incidence of fascitis and empyema different? It would seem to me that a much more logical explanation would be the inclusion of a few critically injured patients in one group *versus* another — and this is a small series of patients — or the fact that one chest tube maybe did not drain the hemothorax quite as well. I would be much more likely just to tote those things up to the vagaries of clinical practice that we all see in taking care of seriously injured patients. In that most severely injured group of patients, which this study does rightly address, I think the authors noted an 11-fold difference in septic complications between the two groups: 3 of 20 in the enteral; 8 of 12 in the TPN. We have already talked about pneumonia and line sepsis, and again a difference of two or three in a group certainly sometimes could be introduced just by bias even, clearly an unintentional bias, would make that "no difference."

I certainly commend the authors on what I think is a good paper, one that fits well with other reports in the literature. But based on clinical experience, I still am not ready to say that every patient who has a serious injury ought to have a J-tube put in, because we clearly find significant jejunostomy complications in our unit. Small bowel obstruction here and there, a tube that gets pulled out of the bowel with resultant peritonitis, diarrhea commonly causing dehydration. Occasionally, in elderly patients, we have seen dead bowel as well.

Finally, neither group had an ultimate improvement in survival. The authors talked a lot about comparative costs but did not look at all factors related to cost, such as nursing time in changing the beds because of increased diarrhea or keeping the enteral feeding tubes open. These are complex issues that must be carefully evaluated. Thank you.

DR. LEWIS M. FLINT, JR. (New Orleans, Louisiana): Thank you, Dr. Bland. Based on some comments that have been made from this platform this afternoon, I feel compelled to point out that the gentleman on my